

- 3299 o Collect information on acute poisonings
- 3300 o Improve analytical methods for biomonitoring and external measurements
- 3301 o Allow researchers to have access to extensive formulation data (solvents, co-
- 3302 formulants, etc.).
- 3303 b) Research potential links between exposure and health outcomes
- 3304 o Characterise substances or groups of substances causing health outcomes
- 3305 o Focus on susceptible individuals or groups of individuals (gene polymorphism of
- 3306 enzymes, ...)
- 3307 o Focus on exposure windows and susceptibility (pregnancy, development)
- 3308 o Bridge the gap between epidemiology and toxicology (mode of action)
- 3309 o Improve knowledge on mixture toxicity
- 3310 o Foster new approaches of research (*in vitro* and *in silico* models, omics, ...)
- 3311
- 3312

3313 **A.3. Similarities and differences between the EFSA External Scientific**

3314 **Report and the INSERM report**

3316 The two reports discussed herein have used different methodologies. Yet, their results and conclusions
 3317 in many cases agree. The INSERM report is limited to predefined outcomes and it attempted to
 3318 investigate the biological plausibility of epidemiological studies by reviewing toxicological data as well,
 3319 meanwhile the EFSA report is a comprehensive systematic review of all available epidemiological
 3320 studies that were published during a 5 year window.

3321 The differences between the reports are shown in Table 9 and are related to the time period of search
 3322 (i.e., both reports did not assess the same body of published data), different criteria for eligibility of
 3323 studies and different approaches to summarising the evidence across and within outcomes. Overall,
 3324 the INSERM report identified a greater number of associations with adverse health effects than the
 3325 EFSA report. However, a well-documented association with pesticide exposure was claimed by both
 3326 reports for the same health outcomes (childhood leukaemia, Parkinson's disease).

Table 9: Comparison between methods used in the EFSA External Scientific Report and the INSERM Report

	EFSA External report	INSERM report
Articles reviewed	602/43000	NR
Language	Yes	NR
Search strategy (key words, MeSH)	Yes	NR
Search database	Yes (4)	NR
Years of publication	2006 to 2012 (Sep)	? to 2012 (Jun)
Type of epi studies assessed	Cross- sectional Case-control Cohort	Cross- sectional Case-control Cohort
Inclusion criteria	Yes	NR
Exclusion criteria	Yes	NR
Methodological quality assessment	Yes (12 criteria)	NR
Exposure groups*	Yes	Yes
Exposure assessment	Yes	Ye
Quantitative synthesis (meta-analysis)	Ye	N
Qualitative synthesis#	Yes	Ye
Supporting Toxicological data	NI	Yes
Associations with individual pesticides	Yes	Yes
<i>Health outcomes studied:</i>		
Haematological cancer	Yes	Yes
Solid tumours	Yes	Yes
Childhood cancer	Yes	Yes
Neurodegenerative disorders	Yes	Yes
Neurodevelopmental outcomes	Ye	Yes
Neuropsychiatric disturbances"	N	Ye
Reproductive and developmental	Ye	Yes
Endocrine	Yes	NI
Metabolism	Yes	Yes
Immunological	Yes	NI
Respiratory	Yes	NI

NR = not reported

NI not investigated

* exposure type (environmental, occupational, etc.) and period (general population, children, etc.)

.. e.g. depressive disorders

add explanation

A.4. The Ontario College of Family Physicians Literature review (OCFPLR)

In 2004, the Ontario College of Family Physicians (Ontario, Canada) reviewed the literature published between 1992 and 2003 on major health effects associated with pesticide exposure. The authors concluded that positive associations exist between solid tumours and pesticide exposures as shown in Table 10. They noted that in large well-designed cohort studies these associations were consistently statistically significant, and the relationships were most consistent for high exposure levels. They also noted that dose response relationships were often observed, and they considered the quality of studies to be generally good.

3348 **Table 10:** Health Effects considered in the Ontario College of Family Physicians review, 2004

3349

Endpoint	Associations identified by the Ontario College, pesticide (if differentiated), study type, (no. of studies/total no. of studies)
A) Cancer	
1. Lung	-ve cohort (1/1) +ve case control (1/1) +ve carbamate, phenoxy acid, case control (1/1)
2. Breast	+ve case-control (2/4) +ve ecological (1/1) +ve triazine, ecological (1/1) -ve atrazine, ecological (1/1)
3. Colorectal	
4. Pancreas	+ve cohort (1/1) +ve case control (2/2)
5. Non-Hodgkin's lymphoma	+ve cohort (9/11) +ve case control (12/14) +ve ecological (2/2)
6. Leukaemia	+ve cohort (5/6) +ve case control (8/8) -ve ecological (1/1) +ve lab study (1/1)
7. Brain	+ve cohort (5), similar case-control (5)
8. Prostate	+ve cohort (5/5) case-control (2/2) ecological (1/1)
9. Stomach	
10. Ovary	
11. Kidney	+ve pentachlorophenol cohort (1/1) +ve cohort (1/1) +ve case control (4/4)
12. Testicular	
B) Non-Cancer	

1. Reproductive effects	+ve glyphosate
Congenital malformations	+ve pyridil derivatives
Fecundity/time to pregnancy	Suggest impaired
Fertility	
Altered growth	Possible +ve association, but further study required
Fetal death	Suggested association
Mixed outcomes	
2. Genotoxic/immunotoxic	+ve Synthetic pyrethroids (1)
Chromosome aberrations	+ve organophosphates (1)
	+ve fumigant and insecticide applicators
NHL rearrangements	+ve fumigant and herbicide applicators
3. Dermatologic	
4. Neurotoxic	
Mental & emotional impact	+ve
Functional nervous system impact	+ ve organophosphate/carbamate poisoning
Neuro-degenerative impacts (PD)	+ve cohort (4/4)
	+ve case control (2/2)
	+ve ecological (1/1)

3350 +ve: positive; -ve: negative

3351

3352 The report concluded that there was compelling evidence of a link between pesticide exposure and the
 3353 development of Non-Hodgkin's Lymphoma, and also clear evidence of a positive association between
 3354 pesticide exposure and leukaemia. The authors also claimed to have found consistent findings of a
 3355 number of nervous system effects, arising from a range of exposure time courses.

3356 Such strong conclusions found favour with Non-Governmental organisations (NGOs) and raised
 3357 questions among some Regulatory Authorities. The Advisory Committee on Pesticides (ACP), at that
 3358 time an UK government independent advisory committee, was asked to provide an evaluation of the
 3359 outcome of the Ontario College review. The committee membership included one epidemiologist and
 3360 the committee consulted five other epidemiologists involved in providing independent advice to other
 3361 government committees. They all agreed that the review had major shortcomings (e.g. exact search
 3362 strategy and selection criteria not specified, selective reporting of results, inadequate understanding
 3363 and consideration of relevant toxicology, insufficient attention to routes and levels of exposure, not
 3364 justified conclusions, etc.). Overall the conclusions of the Ontario College review were considered not
 3365 to be supported by the analysis presented. In 2012 the Ontario review authors published an update of
 3366 their evaluation; in their second report they used a very similar approach but offered more detail
 3367 concerning the inclusion criteria used. This example is a reminder of the risk of over interpretation of
 3368 epidemiological studies. In particular, a causal inference between exposure and the occurrence of
 3369 adverse health effects is often made, but this represents an association that should be further
 3370 assessed.

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Annex B — Human biomonitoring project outsourced by EFSA

In 2015 EFSA outsourced a project to further investigate the role of HBM in occupational health and safety strategies as a tool for refined exposure assessment in epidemiological studies and to contribute to the evaluation of potential health risks from occupational exposure to pesticides. It was in fact recognised that exposure assessment is a key part of all epidemiological studies and misclassification of exposure and use of simple categorical methods are known to weaken the ability of a study to determine whether an association between contact and ill-health outcome exists; at present, this limits integration of epidemiological findings into regulatory risk assessment.

The consortium formed by Risk & Policy Analysts Limited (RPA), IEH Consulting Limited (IEH) and the Health&Safety Laboratory (HSL) carried out a systematic literature review for the period 1990 to 2015 with the aim to provide an overview on the use of HBM as a tool for occupational exposure assessment refinement, identifying advantages, disadvantages and needs for further development (first objective). The search identified 2096 publications relating to the use of HBM to assess occupational exposure to pesticides (or metabolites). The outcome of the search (Bevan et al., 2017) indicated that over the past 10 to 20 years there has been an expansion in the use of HBM, especially into the field of environmental and consumer exposure analysis. However, further improvement of the use of HBM for pesticide exposure assessment is needed, in particular with regards to: development of strategies to improve or standardise analytical quality, improvement of the availability of reference material for metabolites, integration of HBM data into mathematical modelling, exposure reconstruction, improvements in analytical instrumentation and increased availability of human toxicology data.

The contractors performed a review of available HBM studies/surveillance programmes conducted in EU/US occupational settings to identify pesticides (or metabolites) both persistent and not persistent, for which biomarkers of exposure (and possibly effect) were available and validated (second objective). A two-tiered screening process that included quality scoring for HBM, epidemiological and toxicological aspects, was utilised to identify the most relevant studies, resulting in 178 studies for critical review. In parallel with the screening of identified studies, a Master Spreadsheet was designed to collate data from these papers, which contained information relating to: study type; study participants; chemicals under investigation; biomarker quality check; analytical methodology; exposure assessment; health outcome/toxicological endpoint; period of follow-up; narrative of results; risk of bias and other comments.

HBM has been extensively used for monitoring worker exposure to a variety of pesticides. Epidemiological studies of occupational pesticide use were seen to be limited by inadequate or retrospective exposure information, typically obtained through self-reported questionnaires, which can potentially lead to exposure misclassification. Some examples of the use of job exposure or crop exposure matrices were reported. However, little validation of these matrix studies against actual exposure data had been carried out. Very limited data was identified that examined seasonal exposures and the impact of PPE, and many of the studies used HBM to only assess one or two specific compounds. A wide variety of exposure models are currently employed for health risk assessments and biomarkers have also often been used to evaluate exposure estimates predicted by a model.

From the 178 publications identified to be of relevance, 41 individual studies included herbicides, and of these, 34 separate herbicides were identified, 15 of which currently have approved for use in the EU. Similarly, of the 90 individual studies that included insecticides, 79 separate insecticides were identified, of which 18 currently have approved for use in the EU. Twenty individual studies included fungicides, with 34 separate fungicides being identified and of these 22 currently have approved for use in the EU. The most studied herbicides (in order) were shown to be: 2,4-D > atrazine > metolachlor = MCPA > alachlor = glyphosate. Similarly, the most studied insecticides (in order) were: chlorpyrifos > permethrin > cypermethrin deltamethrin > malathion, and the most studied fungicides were: captan > mancozeb > folpet.

Current limitations comprised the limited number of kinetic data from humans, particularly with respect to the ADME of individual pesticides in human subjects, which would allow more accurate HBM sampling for all routes of exposure. A wider impact of this is on the development of PBPK models for